# Applying Digital Technologies to Rare Disease Diagnosis, Care, Treatment and Cure

Michael N. Liebman, PhD

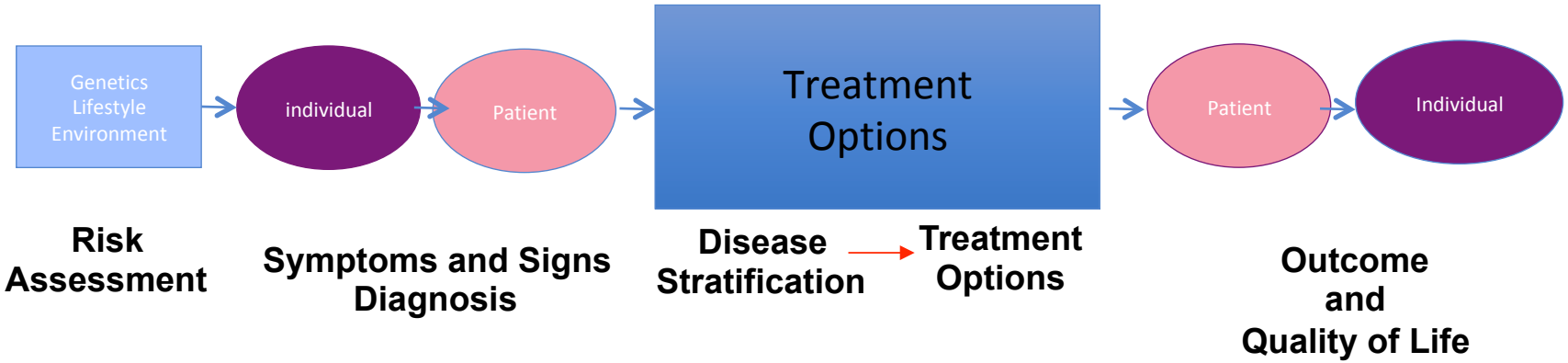
Managing Director, IPQ Analytics, LLC

Professor, Drexel College of Medicine

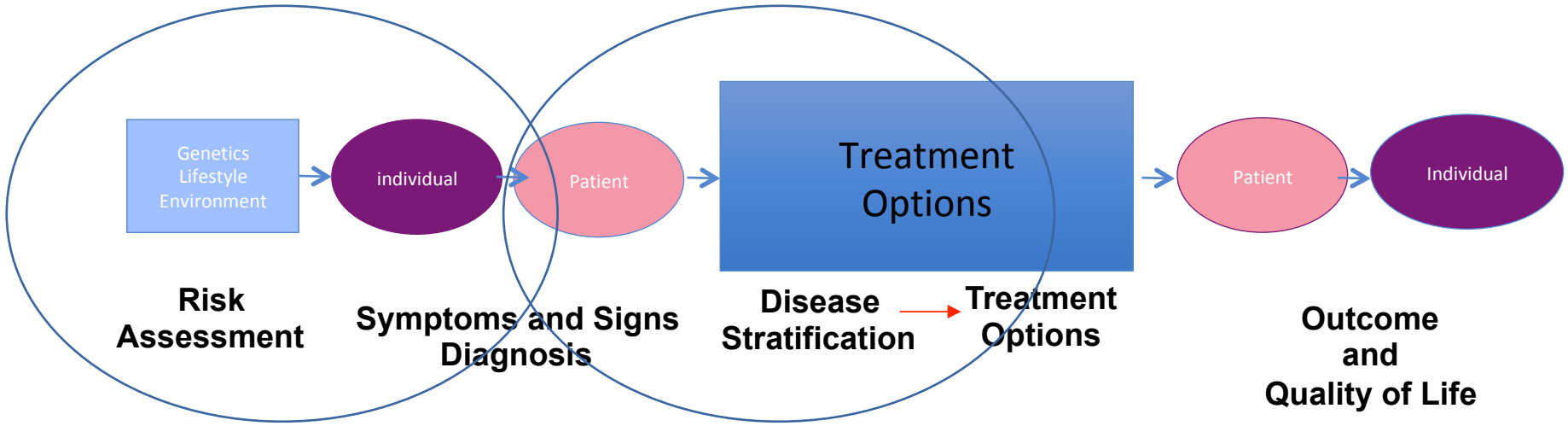
Professor, Wenzhou College of Medicine

Invited Professor, SCBIT, Chinese Academy of Science

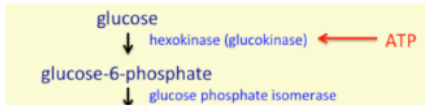
# The Process of Disease

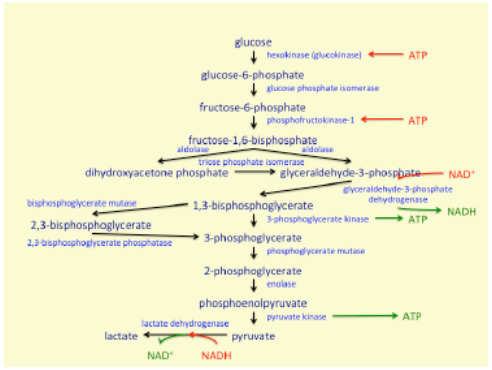


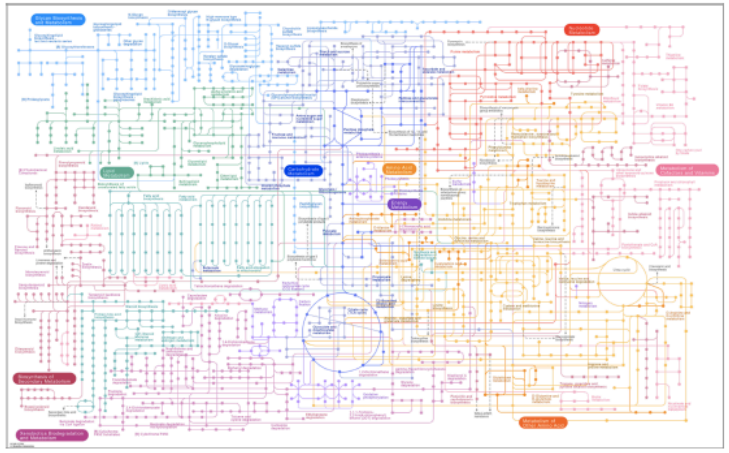
# The Process of Disease



# Simple→Complicated→Complex



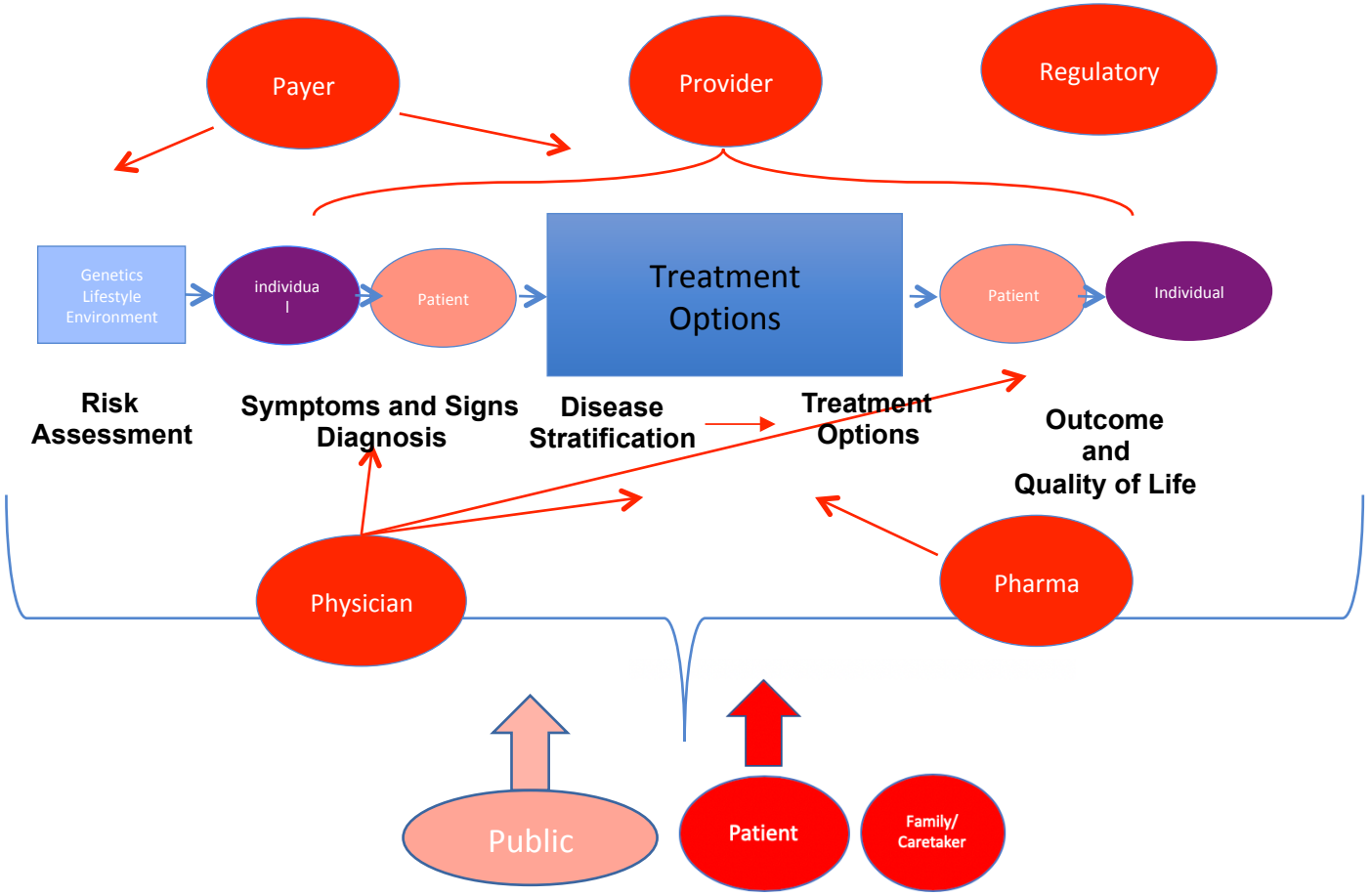



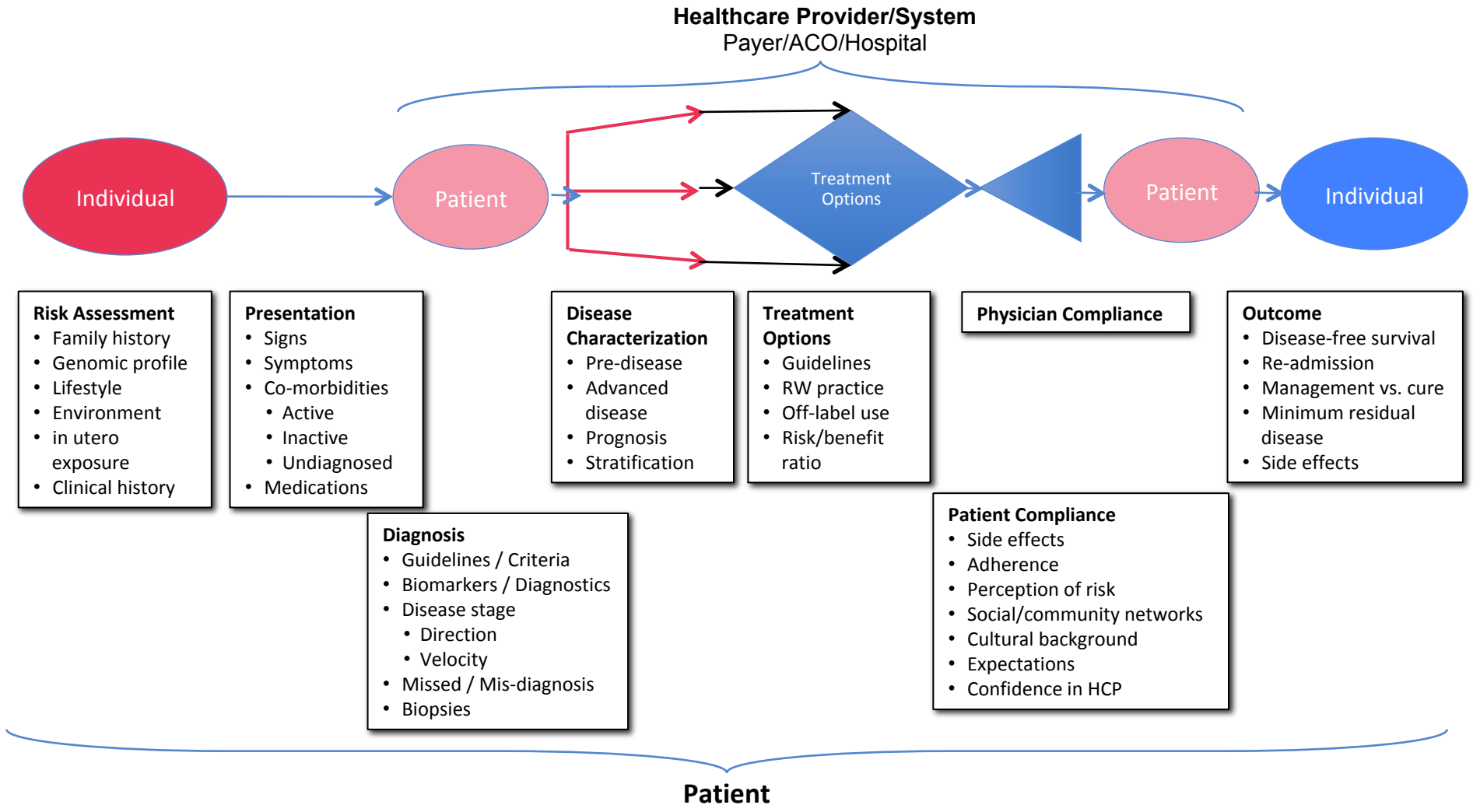
SIMPLE → COMPLICATED → COMPLEX

**Real World patients and disease are Complex!!**

# The Challenge: Different Perspectives and Priorities



# Disease: Real World Data



# Syndrome (Diagnosis vs Guidelines)

Patient 1 **“Diagnosis”**

- Symptom 1 pain
- Symptom 2 anemia
- Symptom 3 …
- Symptom 4 …
- Symptom 5 …
- Symptom 6 …
- Symptom 7 …
- Symptom 8 …
- Symptom 9 …
- Symptom 10 …

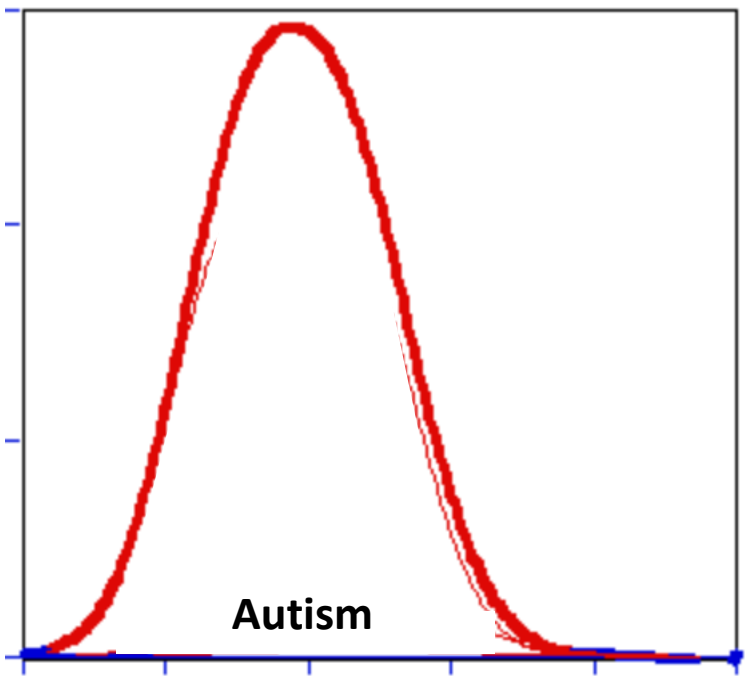
Patient 2 **“Diagnosis”**

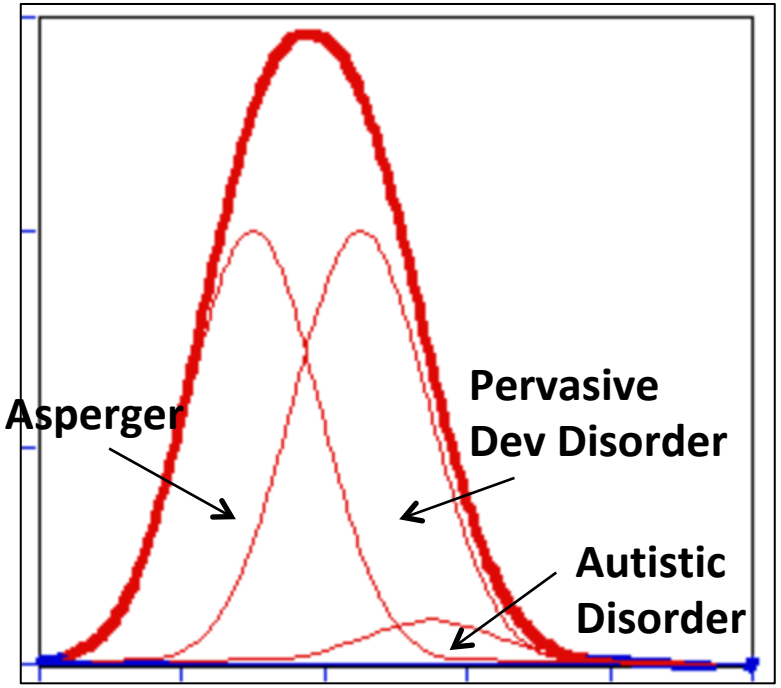
- Symptom 1 pain
- Symptom 2 anemia
- Symptom 3 …
- Symptom 4 …
- Symptom 5 …
- Symptom 6 …
- Symptom 7 …
- Symptom 8 …
- Symptom 9 …
- Symptom 10 …

A 2014 study led by Singh found that **at least one in 20 adult**s in the USA left the doctor's office **with a misdiagnosis**, which equates to 12 million people per year. Half of these misdiagnoses, the authors estimated, are potentially harmful.

# Error in Diagnosis

**IOM Report**
**10% Error in Diagnosis**




**40-50% Error**
**in Disease Stratification**

# Limiting Accuracy of Diagnosis…and Treatment

**Hs Troponin Assay Leads to Overdiagnosis of MI?**
Batya Swift Yasgur MA, LSW. March 27, 2019

Using a high-sensitivity cardiac troponin 1 (hs-cTnI) assay to diagnose myocardial infarction (MI) may lead to **overdiagnosis with resulting inappropriate therapies**.
Studies on 20,000 consecutive inpatients found that 1 in 20 had levels of troponin exceeding the recommended upper limit of normal (ULN) and showed no clinical signs or symptoms of MI

**New Dementia Subtype That Mimics Alzheimer's Identified**
Megan Brooks May 03, 2019
Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a specific type of dementia that **mimics Alzheimer disease** (AD) but is caused by TDP-43 protein deposits in the brain rather than beta-amyloid accumulation and mostly affects
people older than 80 years

# Genetic Disorders

A genetic disorder is a disease caused in whole or in part by a change in the DNA sequence away from the normal sequence. Genetic disorders can be caused by a

1) **mutation in one gene** (monogenic disorder)
2) **mutations in multiple genes** (multifactorial inheritance disorder)
3) **combination of gene mutations and environmental factors**
4) **damage to chromosomes** (changes in the number or structure of entire chromosomes, the structures that carry genes)

NIH National Human Genome Research Institute

# One in five 'healthy' adults may carry disease-related genetic mutations

By Ryan Cross | Jun. 26, 2017 , 6:15 PM

ORIGINAL RESEARCH | 1 AUGUST 2017

# The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients: A Pilot Randomized Trial

*Jason L. Vassy, MD, MPH, SM; Kurt D. Christensen, PhD, MPH; Erica F. Schonman, MPH; Carrie L. Blout, MS, CGC; Jill O. Robinson, MA; Joel B. Krier, MD; Pamela M. Diamond, PhD; Matthew Lebo, PhD; Kalotina Machini, PhD; Danielle R. Azzariti, MS, CGC; Dmitry Dukhovny, MD, MPH; David W. Bates, MD, MSc; Calum A. MacRae, MD, PhD; Michael F. Murray, MD; Heidi L. Rehm, PhD; Amy L. McGuire, JD, PhD; Robert C. Green, MD, MPH,; for the MedSeq Project **

Michael Snyder, director of the Stanford Center for Genomics and Personalized Medicine in Palo Alto, California, and colleagues found that 12 out of 70 healthy adults, or **17%, unknowingly had one or more DNA mutations that increased the risk for genetic diseases** for which there are treatment or preventative options.

**High Frequency Actionable Pathogenic Exome Mutations in an Average-Risk Cohort**

Shannon Rego, Orit Dagan-Rosenfeld, Wenyu Zhou, M. Reza Sailani, Patricia Limcaoco, Elizabeth Colbert, Monika Avina, Jessica Wheeler, Colleen Craig, Denis S alins, Hannes L. Röst, Jessilyn Dunn, Tracey McLaughlin, Lars M. Steinmetz, Jonathan A. Bernstein, Michael P. Snyder

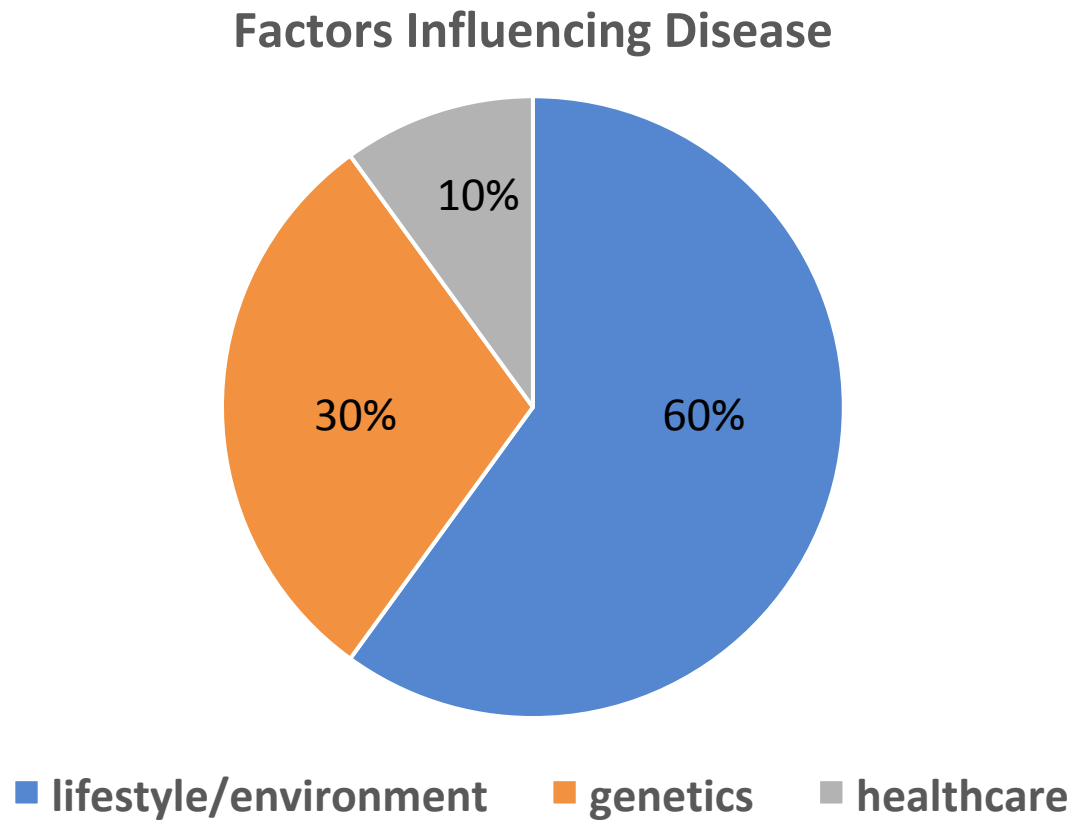
"We used American College of Medical Genetics (ACMG) guidelines were used for the classification of rare sequence variants, and additionally we assessed pharmacogenetic variants. Twelve out of 70 (17%) participants had medically actionable findings in Mendelian disease genes, including 6 (9%) with mutations in genes not currently included in the ACMG's list of 59 actionable genes.

# Genomics + lifestyle/environment → rare disease

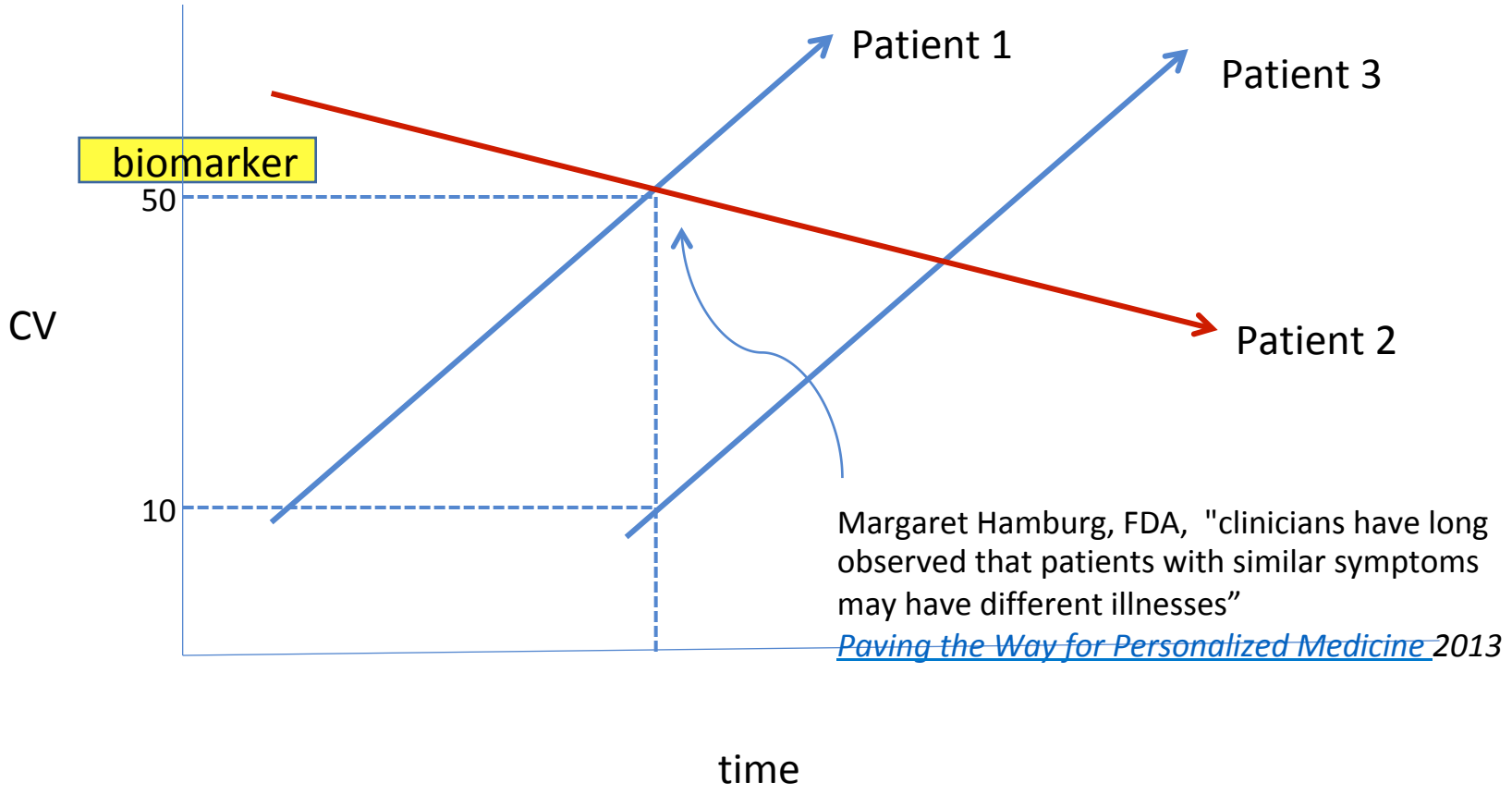
New York Times, Health & Science April 24, 2019

**For three years her skin ulcers and pain would flare, then vanish, stumping doctors. Her daughter, a nurse, finally figured it out.**

Ho called her cousin, who had recently graduated from medical school, and asked him if he'd ever heard of **Behcet's, which is believed to result from a combination of genetic and environmental factors**.

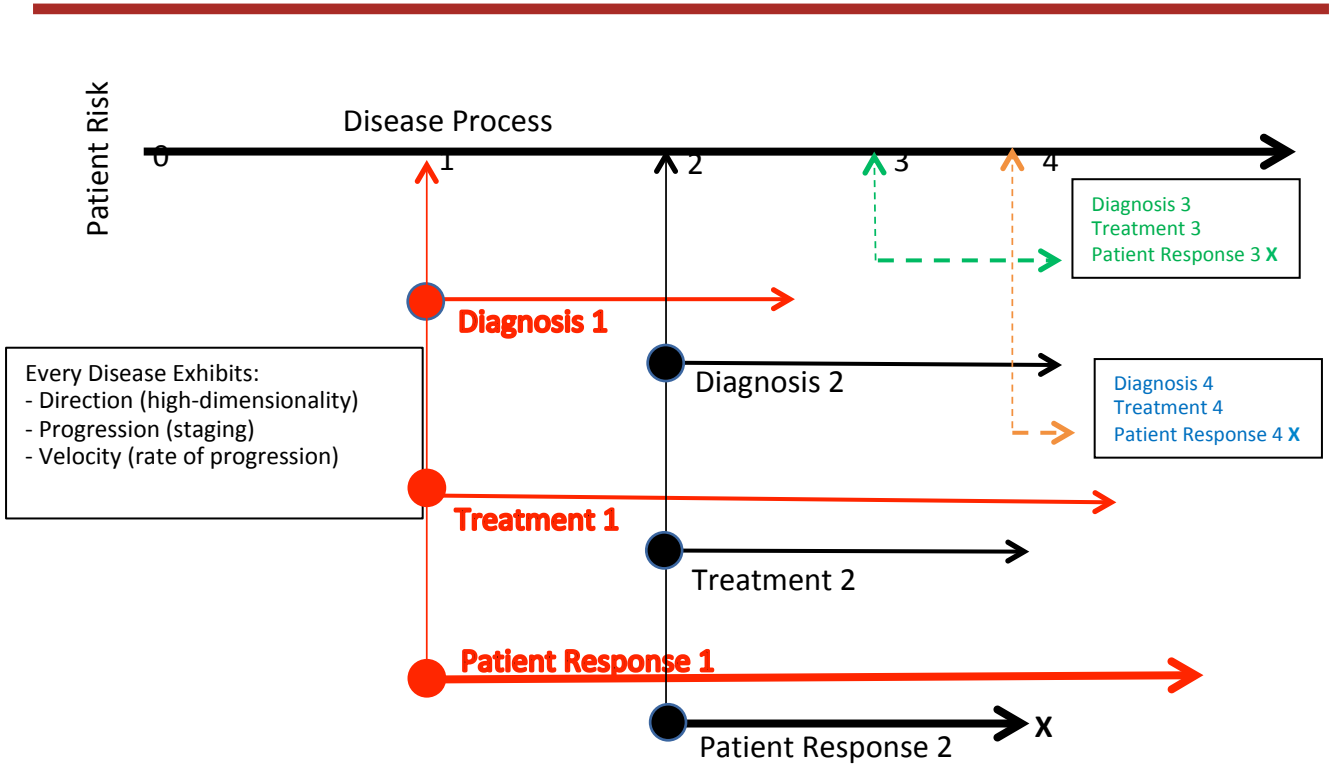

Factors Influencing Disease
10%
30%
60%
lifestyle/environment
genetics
healthcare

# Ambiguity in Diagnosis and Staging

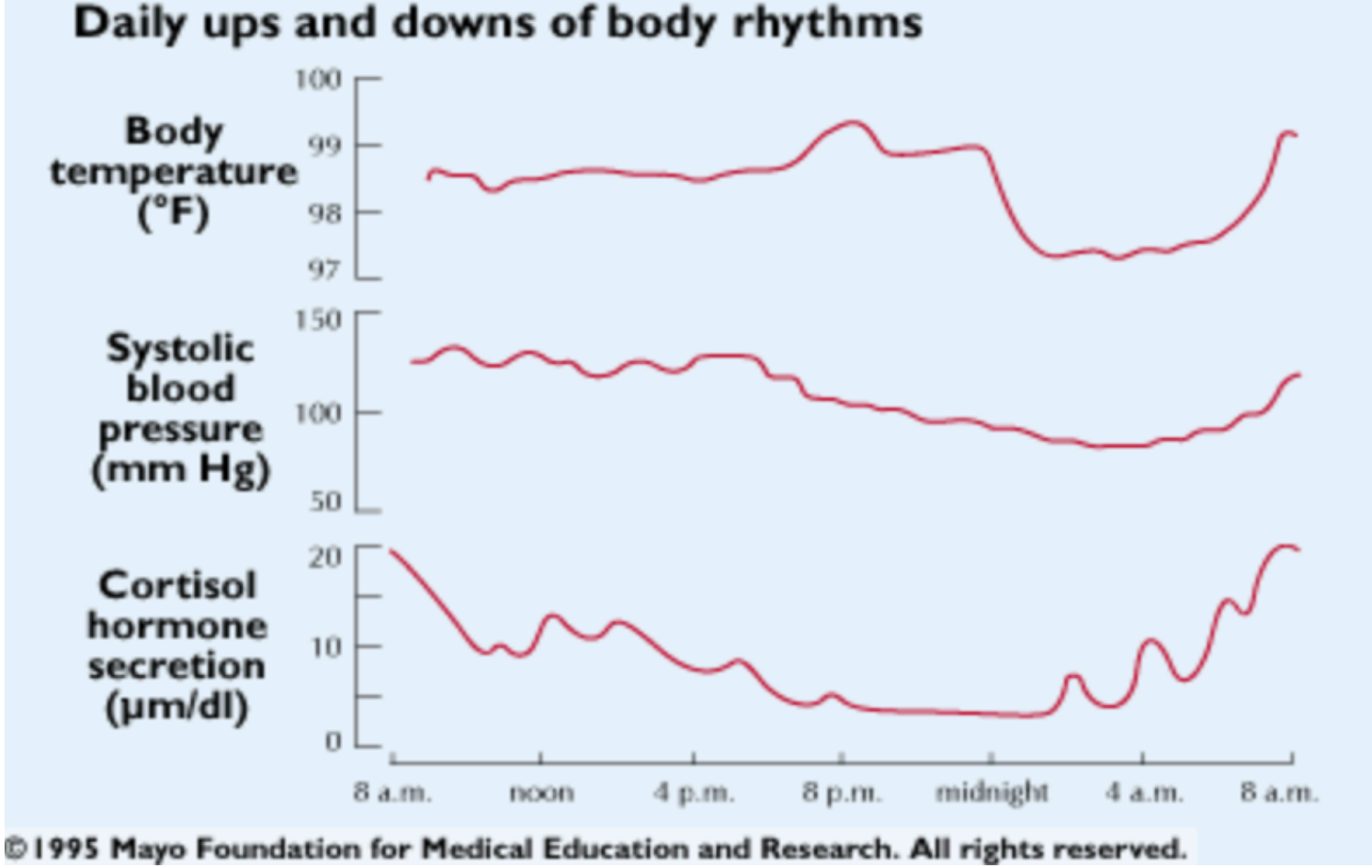



Margaret Hamburg, FDA, "clinicians have long observed that patients with similar symptoms may have different illnesses"
*Paving the Way for Personalized Medicine 2013*

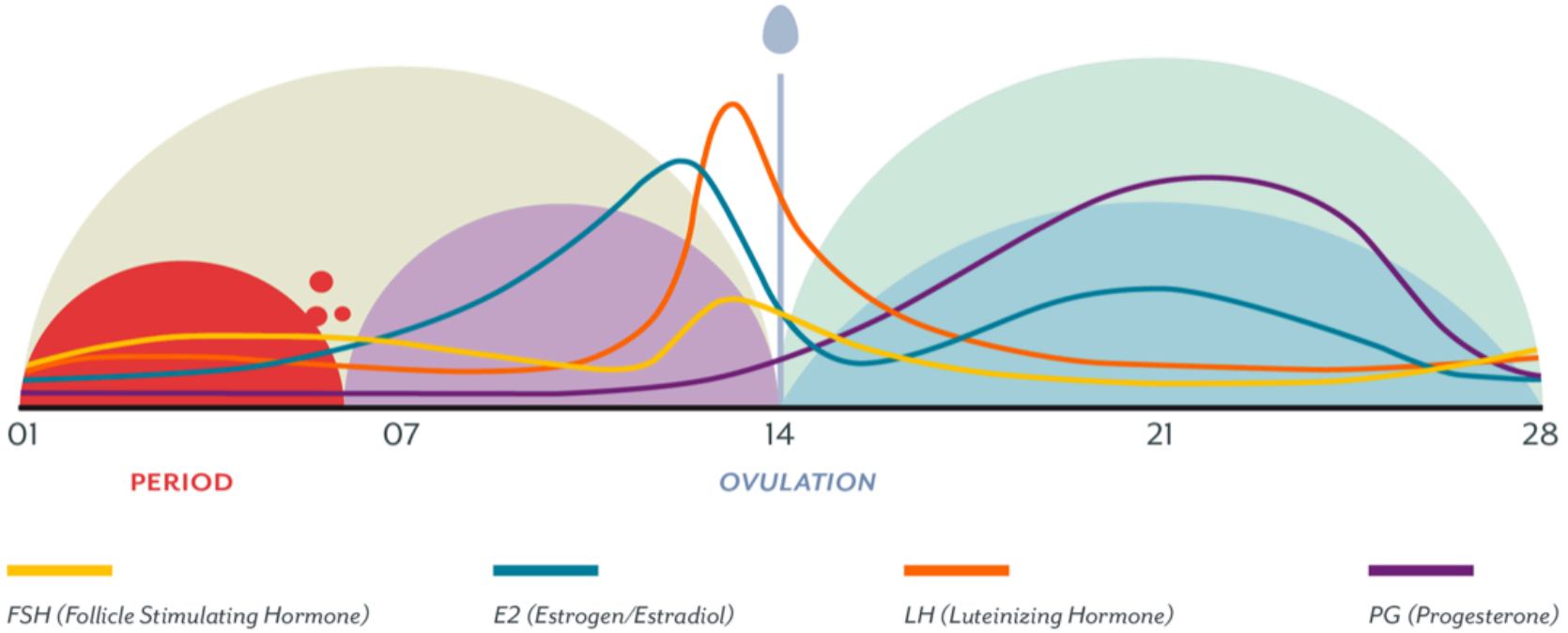
# Disease is a Process, Not a State



# Hourly



# Daily


01
07
14
21
28
PERIOD
OVULATION
FSH (Follicle Stimulating Hormone)
E2 (Estrogen/Estradiol)
LH (Luteinizing Hormone)
PG (Progesterone)

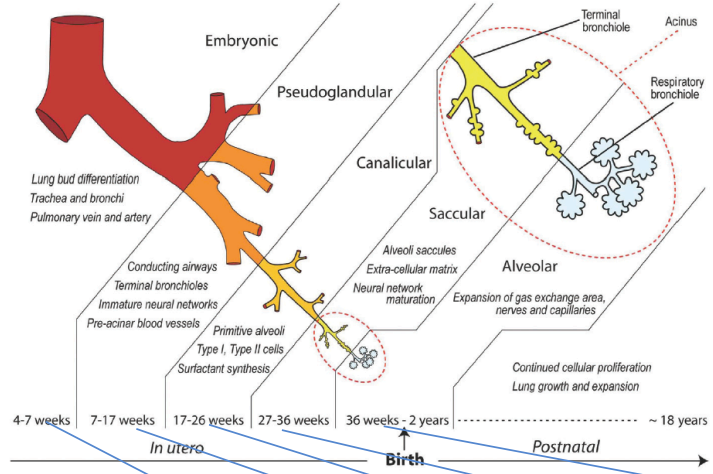
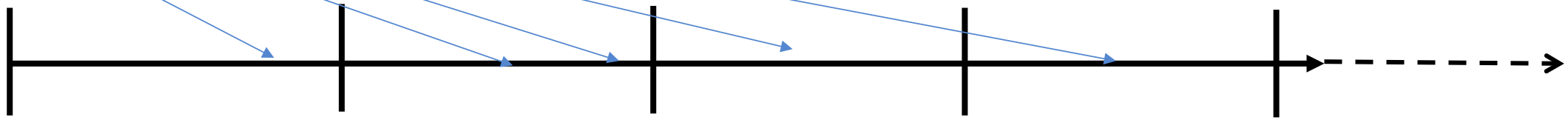



**Figure 2.** Principal stages of lung development in humans: diagrammatic representations of the timeline and developmental organization of trachea, primary bronchi, intrapulmonary bronchi, and acinus in the mammalian respiratory system. Reprinted from *Pharmacology and Therapeutics*, Vol 114 (Kajekar R. 2007. Environmental factors and developmental outcomes in the lung. Pharmacol Therap 114:129–145), copyright (2007), with permission from Elsevier.

# Monthly…

Developmental Processes



0 weeks
Conception

10 weeks

20 weeks

30 weeks

40 weeks
Birth

Developmental Stages

Lifestyle

Environment

# Digital Health will:

- Generate comprehensive and reproducible data
- Establish baseline behaviors with critical observation of normal fluctuations over time, for individuals and populations
- Enable earlier identification of abnormal patterns
- Enhance disease stratification based on clinical observations
  - Improve target selection for drug development
  - Integrate into clinical decision support systems
  - Support monitoring of response to therapy
  - Early warning for adverse events

# One gene mutation, two diseases, many insights into human heart function

## Research on a gene mutation that causes holes in the hearts of infants revealed insights into how the heart develops and how it stays healthy

*Date:* December 15, 2016

*Source:* Gladstone Institutes

*Summary:* Scientists have linked a single gene mutation to two types of heart disease: one causes a hole in the heart of infants, and the other causes heart failure. Using cells donated by a family with the mutation, the researchers gained insight into congenital heart disease, human heart development, and healthy heart function.